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Office of Nutritional Products, Labeling & Dietary Supplements
Food and Drug Administration
Center for Food Safety and Applied Nutrition
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Phyto-derived Ceramides

New Dietary Ingredient Notification (under 21 C.F.R. Sec. 190.6)

Submitted by:

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New Dietary Ingredient Notification:

For Phyto-Derived Ceramides

Introduction and Background

This New Dietary Ingredient ("NDI") Notification is submitted pursuant to 21 C.F.R. § 190.6 and Section 8 of the Dietary Supplement Health and Education Act. This Notification concerns the new dietary ingredient phyto-derived Ceramides, a type of lipids which are constituents of sphingolipids, and for this Notification, derived from either wheat or rice (henceforth Ceramide or Ceramides). Currently, in its research and development for a dietary supplement containing this new dietary ingredient, Soft Gel Technologies, Inc. ("SGTI") of Los Angeles, California is using Cennamides™ (a phyto-derived Ceramide, sourced from wheat germ). Cennamides™ is manufactured by Ennagram of Pantin, France, for SGTI, which intends to use this ingredient in a dietary supplement to promote and support healthy skin. For a proposed new dietary supplement, SGTI intends to use as an ingredient Ceramides derived from either rice or wheat germ oil, in amounts of 30 mg per serving, and 60 mg per day.

The safety evidence presented in this Notification will show that: 1) plant Ceramides are naturally-occurring in many foods; 2) six forms of Ceramides are found in the skin, and these and the various forms of phyto-derived Ceramides are chemically identical or substantially equivalent (please see below); 3) two LD-50 tests detailed below have been performed, one using Cennamides™ (15% Ceramide in wheat germ oil) and one using rice-derived Ceramide and both conclude that the LD-50 is more than 5,000 mg per Kg.; 4) other animal studies also show no toxicity; 5) human efficacy studies using orally-administered Ceramides have been done, and they show no reported adverse events; 6) Ceramides are similar to plant sterols, which the FDA accepts as GRAS in foods; and 7) nutritional supplements and functional foods containing Ceramide (derived from plant sources, e.g., rice bran and wheat) are currently on the market in Japan and have been for approximately 5 years. This Notification is intended to meet the standard of safety for a new dietary ingredient of rice-derived Ceramides as well as for Cennamides™ (wheat-based), collectively Ceramides. In this Notification, SGTI will present the scientific evidence and substantiation on which it bases its conclusion that a dietary supplement containing Ceramides (in amounts up to 60 mg per day) is reasonably expected to be safe.

Ceramides Found in and Derived from Foods, Plants

Ceramides are found naturally in many foods, especially wheat flour.[1] (Copies of all articles and reported cited or referenced in this Notification are attached.) The amounts of Ceramides in food vary considerably, but considering all the food sources, the per capita Ceramide consumption in the United States is estimated to be 0.3 to 0.4 grams per day.[2,3,4] Sphingolipids, which contain Ceramides, as shown below, are found in large amounts in dairy products, eggs and soybeans.[5] Ceramides are also found in rice, millet, and spinach.[6] By one estimate, sphingolipids account for .01 to .02% of the human diet.[7]

Currently there are many types of Ceramides on the market (e.g., in Europe and Japan) and virtually all of them are commercially derived from plant sources. Ceramides derived from plants (Phyto-Derived Ceramides) are the focus of this Notification, specifically those derived from wheat and rice. Originally Ceramides were derived from soybeans and bovine sources. However, unlike bovine-derived animal Ceramides, which can carry the problematic risk of viral infection or of conditions such as mad cow disease, plant-based Ceramides are attractive from a safety and low risk

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[1] Schmelz, E.V., Uptake and Metabolism of Sphingolipids in Isolated Intestinal Loops of Mice, J. of Nutrition, Vol. 124(5), p. 702, 1994 ("Schmelz").

[2] Merrill, A.H., Jr. *et al.* Sphingolipid Uptake by Isolated Segments of the Rat Intestine, FASEB Journal, P. 3A, 469, 1989 ("Merrill 1989").

[3] Futerman, A. H., Ceramide Metabolism Compartmentalized in the Endopalsmic Reticulum and Golgi apparatus, Chapter 4, Current Topics in Membranes, Vol. 40, p. 93, 1994 ("Futerman").

[4] Lati, E., Special Topic: New Research and Development in Moisture Retention Mechanism and Moisturizing Agents: Phyto-ceramides and their Applications, Fragrance Journal, Vol. 23 (1), No. 81, pp. 1-14, at p.1, 1995 ("Lati").

[5] Vesper, H. *et al.* Sphingolipids in Food and the Emerging Importance of Sphingolipids to Nutrition, J. of Nutrition, Vol. 129: pp. 1239-1250, 1999 ("Vesper"); Berra, B. *et al.*, Dietary Sphingolipids in Colorectal Cancer Prevention, Eur. J. of Cancer Prev., Vol. 11, pp. 193-197, at p. 193, 2002.

[6] Lati at p. 2.

[7] Hoang, T., Sphingolipids (a Powerpoint presentation), March 28, 2002, p. 12; also citing to Vesper. Tinyee Hoang is a Graduate Student in Food Science at Washington State University.

standpoint.[8] Now, fermentation processes from yeast and glycerol are available. Two popular sources are brown rice and wheat germ extracts. These are the two common sources of commercially available Ceramide for dietary supplement and cosmetic applications.[9]

Specifically, the subject of this Notification is Ceramides derived from wheat germ, other wheat sources, and from rice; regardless of derivation, these Ceramides are chemically very similar and are substantially equivalent for purposes of safety analysis.[10] The complex plant sphingolipids which make up the ceramide have glucose, galactose, and inositol backbones. Wheat derived ceramides are structurally similar to rice derived ceramides because they share common sugar components and only differ in the placement of the fatty acid component along the chain. This makes these two forms of plant ceramides interchangeable as functional components of a specific sphingoloid (ceramide) class.[11]

Recommended Conditions of Use in the Proposed Product

There are no special requirements for use in dietary supplements containing Ceramides, such as the need to take it on an empty stomach. No suggested conditions for use are required or recommended by SGTI. Most probably, SGTI will place the following Caution on the label of the dietary supplement containing Ceramides: _____ However, this would be purely as a precaution; as shown herein, Ceramides are naturally-occurring in many foods. Again, sphingolipids account for .01 to .02% of the human diet;[12] and Ceramides account for .3 to .4 mg per day in the human diet. Ceramides are neither hormones nor stimulants. Furthermore, there are no limits on the duration of use. Ceramides can be taken for a long term supplementation regimen to keep the skin moist and healthy. SGTI's recommended ingested amount is_____

[8] Lati at p. 1-2.

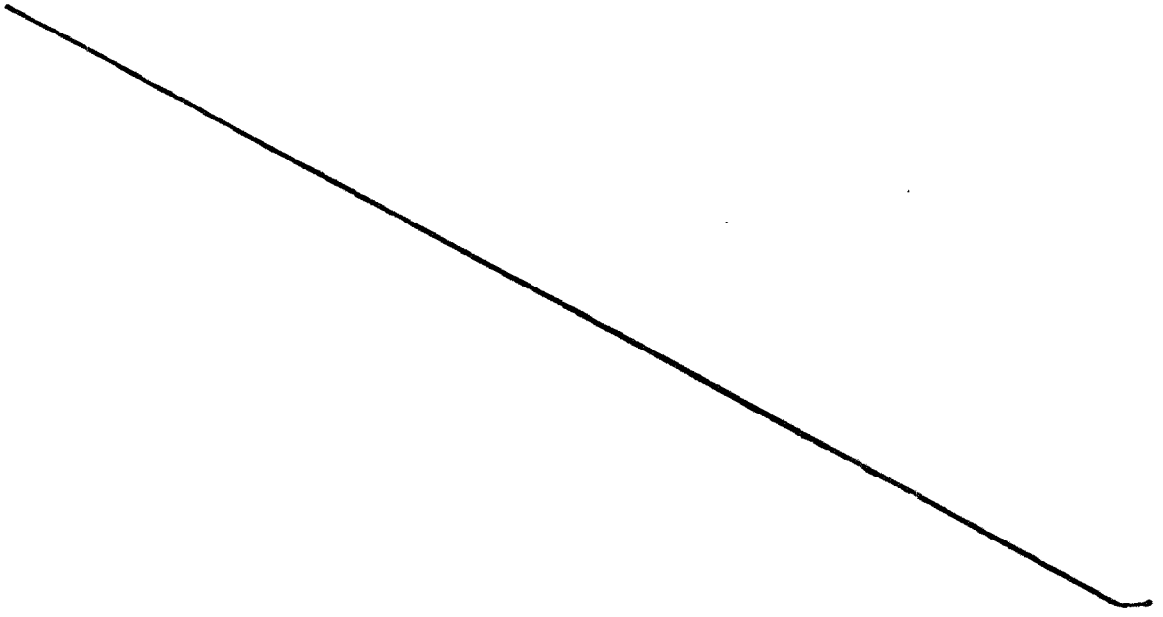
[9] Schmelz, Merrill 1989, Futerman, and Lati.

[10] See, e.g., Lati.

[11] Vesper.

[12] Hoang.

Commercial Manufacturing Process



History on the Discovery and Safe Use of Ceramides

As far back as 1853, scientific papers were published explaining the role of internal lipids (fats) in the skin.[14] Nearly twenty years later, classes of lipids named Sphingolipids were discovered. Specifically, the presence of ceramides as a category within Sphingolipids was "first detected in the animal (human) brain by the German physician L.T. W. Thudichen in 1884, and subsequently these substances were extracted from sources such as the bovine brain for use in cosmetics, etc."[15] Over a century later, much of the biochemistry of lipids in the skin has received

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[13] In-house report of Kenko Corporation for the Manufacturing Process of Cennamide CERP50 (Confidential, Trade Secret information disclosed for the purpose of this Notification to the FDA only.)

[14] Vesper, Oryza Brochure.

[15] Kajimoto, O. *et al.*, Clinical Investigation of the Skin Beautifying Effects of a Beauty Supplement Containing Rice Derived Ceramides-Objective Assessment of Dry Skin through Analysis of Three Dimensional Microscopy Images. Authors are affiliated with the Health Management Center, Osaka University of Foreign Studies; Dermatology Department, Faculty of Medicine, Osaka City University; and the Institute of Comprehensive Medical Science (undated publication) at p. 2 ("Kajimoto").

significant attention and is much better understood. As discussed below, Ceramides are a special class of sphingolipids and are found in the stratum corneum, the outermost skin layer. They account for about 40-65% of lipids in the stratum corneum. There are six kinds of Ceramides found in the skin, all serving different purposes. Ceramides are not very soluble, thus making them difficult to manufacture. They work when absorbed into the stratum corneum, and that mechanism necessitates special processing procedures to derive a viable product for human ingestion and topical use. [16]

Much has been written about "anti-aging" creams and lotions, and more have been sold in recent years based on the current marketing of beauty creams, which promise youthful skin. Aggressive marketing and promising cosmetic formulas have characterized much of this sales boom. The term "anti-aging" is important in establishing the market for Ceramide products. In the early 1990's, major cosmetic companies such as Elizabeth Arden formulated and branded products based on the safe and effective use of Ceramides for treating aging problems such as fine lines, wrinkles, and dryness. These were often in the form of expensive topical creams and potions. Because of its moisture retaining properties, Ceramides were eventually included in cosmetic products such as foundations and lipsticks to increase outer moisture and to provide a benefit to the skin while protecting it from damaging elements.[17] For the same purpose, but via a different route-ingested-SGTI is developing Ceramide-containing dietary supplements.

Ceramides, Sphingolipids and Glycosphingolipids

Ceramides are a type of sphingolipids, which are lipid substances present in all cell structures. Ceramides are constituents of cells in the cytoplasmic membranes. Thus, they are

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[16] Imokawa, G., Structures and Functions of Stratum Corneum Lipids in the Skin, Journal Japan Oil Chem. Society, Vol. 44, No. 10, pp. 1-23, esp. pp. 1, 6 (1995) ("Imokawa"); Lee, M., Analysis of Ceramides in Cosmetics by Revised-Phase Liquid Chromatography/ Electrospray Ionization Mass Spectrometry with Collision-Induced Dissociation, Rapid Commun. Mass Spectrom, 17:64-75 (2003) ("Lee"); Goldstein, A., Ceramides in the Stratum Corneum: Structure, Function, and New Methods to Promote Repair, Int. J. of Derma., Vol. 42, p. 256-259, 2003 ("Goldstein"); and Chamlin, S.L., *et al.* Ceramide-Dominant Barrier Repair Lipids Alleviate Childhood Atopic Dermatitis: Changes in Barrier Function Provide a Sensitive Indicator of Disease Activity, Journal of Am. Acad. Dermatol, Volume 47, No. 2, PR 198-208, 2002 ("Chamlin").

[17] See, e.g., Zetterstern, E., Optimal Ratios of Topical Stratum Corneum Lipids Improve Barrier Recovery in Chronologically Aged Skin, Journal of American Academy of Dermatology, Volume 37, Number 3, Part 1, 1997.

naturally found in the skin, central nervous system, and spinal marrow.[18] As shown above, Ceramides are also present in the plant world, with the main sources being wheat, rice, soy, and spinach. These compounds are the result of the formation of an amide bond between a fatty acid and sphingosine, or phytosphingosine.

Glycosphingolipids (GSLs) are a varied and diverse class of molecules which consist of a sugar attached to Ceramide moieties. More than 400 species are known, though only seven monosaccharides are found in vertebrates. Distributed mainly at the surface of the cell, they participate in the regulation of the interactions of cells with their environment.[19] These lipids serve as distinguishing markers for cells and mediate cell-to-cell recognition and communication. They are essential for the development and growth of organisms, and their decrease has been implicated in skin disease,[20] and in a number of serious diseases such as cancer and viral infections.[21,22,23]

The separation of GSLs into groups and subgroups is made according to the different kinds of carbohydrates, acyl, or sphingosine structures which can attach to form a variety of compounds. GSLs are commonly divided into two main groups, Neutral GSLs and Acidic GSLs. Acidic GSL compounds reflect the type of structures which form the basis of the Ceramide compounds which are the subject of this NDI Notification.

Ceramides are the simplest sphingolipids and situated at the center of sphingolipid metabolism. Thus, the transfer of a phosphorylcholine head group from phosphatidylcholine to Ceramide yields another phospholipid, sphingomyelin (also sphingolipid); and the addition of carbohydrate groups from the sugar donor, UDP-hexose, yields complex Glycosphingolipids (cerebrosides, sulfatides, gangliosides). These compounds can be converted back to Ceramide by the

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[18] Lati at p. 1.

[19] Goldstein.

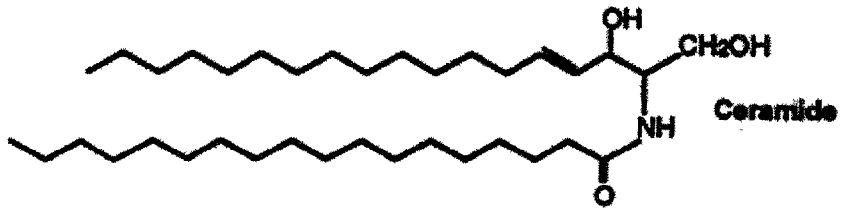
[20] Kajimoto at p. 1.

[21] Goldstein, p. 256.

[22] Yamamura, T. and Tekezuka, T., Change in sphingomyelinase activity in human epidermis during aging, Journal of Dermatological Science, 1(2): p. 79-84, 1990 ("Yamamura").

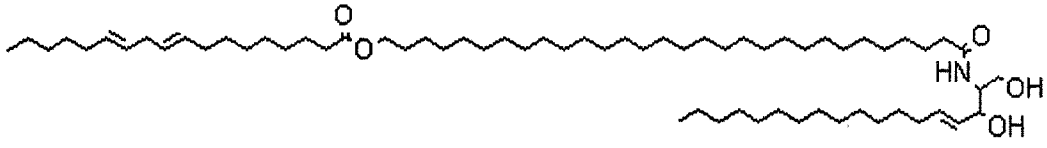
[23] Merrill, A.H., Jr. *et al.*, Importance of Sphingolipids and Inhibitors of Sphingolipid Metabolism as Components of Animal Diets, Journal of Nutrition, Vol. 127, pp. 830S- 833S, 1997 ("Merrill 1997").

removal of sugars (glycosidases) or phosphorylcholine by sphingomyelinases. An enzyme (ceramidase) is able to cleave the amide-linked fatty acid of ceramide and free sphingosine.



Free ceramides are separated with the neutral lipid fraction on a silica column; and the minute amounts present in cell extracts are best analyzed after derivatization before HPLC. Their chromatographic behavior is not very different from that of diacylglycerols which are also structurally similar. The amide linkage is resistant to hydrolysis but is disrupted by prolonged heating in an alkaline medium (although better with an acidic reagent). Ceramide can be prepared conveniently from complex Glycosphingolipids by chemical degradation.[24]

The stratum corneum of the skin (the upper-most layer made of dead cells) has a unique lipid composition which comprises mostly free fatty acids, cholesterol and ceramides (O-acylceramides). These are different molecular species, differing by the head group architecture and by the mean fatty acid chain length. The fatty acid esterified to the amide of the (phyto)sphingosine head group can be either a-hydroxy or nonhydroxy fatty acids. The fatty acid chain length varies from 16 to 34 carbon atoms. [25] One Ceramide (figure below) contains linoleic acid linked to the long chain (n=30) □-hydroxy fatty acid. This molecule is thought to be of importance for proper skin barrier function.[26]



[24] Orgretmen, B. *et al.*, Biochemical mechanisms of the generation of endogenous long chain ceramide to exogenous short chain ceramide in A549 human lung adenocarcinoma cell line, J. of Bio. Chem., Vol. 227, No. 15, 2002 ("Orgretmen").

[25] Bouwstra, J.A. *et al.*, Role of ceramide 1 in the molecular organization of the stratum corneum lipids. J. Lipid Res., 39(1), pp. 186-96, Jan. 1998 (Abstract from PubMed).

[26] Brochure entitled Oryza Ceramide, Nutritional Supplement, from Oryza Oil & Fat Chemical Co. Ltd, called in the footer: ORYZA CERAMIDE CATALOG ver. 1.0EZ ("Oryza brochure").

Orgretmen explains how endogenous ceramide found in skin mediates the action of exogenous ceramide. This action is thought to work via a recycling process where the sphingosine backbone of Ceramide is thought to be recycled. This provides the link which allows phyto-derived ceramide compounds to be used to replace degraded ceramide which is depleted in the stratum corneum.[27] As stated above, Ceramides are commercially extracted from rice bran or wheat germ. These plant sources naturally contain a large amount of glycosphingolipids. The glycosphingolipids of rice bran are similar to the animal glycosphingolipids, in which the backbone of the Ceramide including sphingoid bases with fatty acids is an amide linkage, and the terminal hydroxyl group is substituted by glucose. Glycosphingolipids have a great variety of molecular species because of the partial structure of sphingoid bases.[28]

Ceramide Functionality and Efficiency

Ceramides are also natural components of human skin.[29] There are six Ceramide species or structures commonly found in skin.[30] These Ceramides are formed via a biosynthetic mechanism in the epidermis. The four layers of the epidermis contain Ceramides, and they play an important role by creating a barrier which reduces infection and helps to retain the skin's moisture.[31] Reduction in the amount of Ceramides in the epidermal layers results in dry skin, dermatitis, and is believed to be a major cause of wrinkles.[32] Studies have shown that a proper amount of Ceramides in the internal epidermal layer is necessary to maintain healthy skin.[33,34,35]

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[27] Orgretmen.

[28] Schmelz, Merrill 1989, Futerman, and Lati.

[29] Imokawa.

[30] Imokawa at p. 3.

[31] Imokawa at pp. 6-9.

[32] See, e.g., Lati at pp. 5-6.

[33] Futerman and Lati; Zetterstern, E., Optimal Ratios of Topical Stratum Corneum Lipids Improve Barrier Recovery in Chronologically Aged Skin, Journal of American Academy of Dermatology, Volume 37, Number 3, Part 1, 1997 ("Zetterstern").

[34] Chamlin.

[35] Yamamura.

The stratum corneum is the outermost layer of mammalian skin. This layer primarily acts as a barrier to protect us from external environmental stresses and to prevent excessive transcutaneous water loss. The cells of the stratum corneum, corneocytes, and the lipids between them, Ceramides, accomplish this important function. Disruptions of this barrier, through either physical trauma caused by dermatitic conditions like eczema or by simple aging, results in this important function being compromised. The result is decreased elasticity, increased susceptibility to infection, and increased water loss which can lead to aging conditions such as wrinkles and fine lines, as well as an overall dullness to the skin's texture.[36,37]

Plants contain structures which are chemically similar to human Ceramides. These plant-derived, or phyto-derived, Ceramide products can aid in creating the protective barrier in the epidermis. Supplementation with an oral agent of Ceramide replaces the components lost through aging, and has hydration effects.[38] The moisturizing effect comes from the Ceramides being carried directly to the stratum corneum via the blood. This direct method improves the functionality of the Ceramides and produces results not seen in cosmetic topical applications.[39]

Ceramides have become an important compound for skin protection. Lipid depletion and replenishment studies have shown that Ceramides play an essential role in establishment and maintenance of the water-retaining properties of skin. Since it is known that Ceramides decrease with age, it has been suggested that increased transepidermal water loss is the result of their reduced presence in the skin. In short, Ceramides play an important role in preventing moisture loss which can be caused by physical trauma or aging.[40]

It is also known that Ceramides inhibit Melanogenis and are thought to promote a pigment lightening effect. Melanogenis is a process by which the skin produces pigments that give our skin

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[36] Imokawa, Goldstein, and Yamamura.

[37] Lee.

[38] Lati at p. 6.

[39] Imokawa, Lee, Goldstein, and Yamamura.

[40] Imokawa, Lee, Goldstein, and Yamamura.

its unique tone and color. This is particularly helpful for hyper-pigmentation which causes age spots and other discolorations of the skin. In an *in vitro* study using B-16 melanoma cells, the melanogenic effect of Ceramides was observed. Ceramides exhibited a stronger whitening effect when compared to ascorbic acid, arbutin, and ellagic acids.[41, 42]

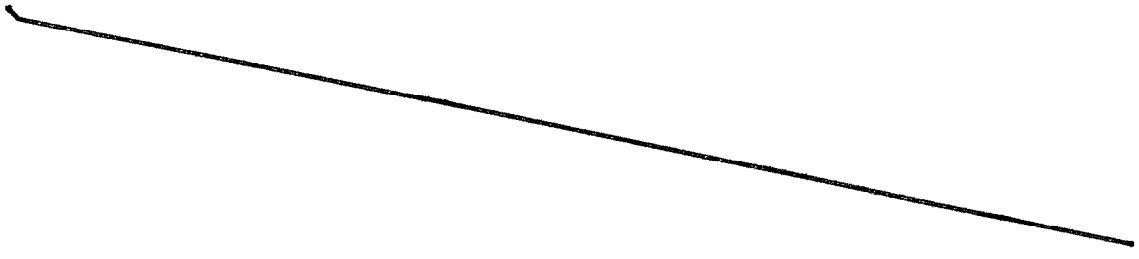
The moisturizing effect of Ceramide was established in several clinical studies. These studies show that Ceramide is absorbed via the digestive system and carried to the stratum corneum by blood, where it circulates, and produces a significant effect in promoting a water barrier in the layers of the skin. Therefore, Ceramides in the stratum corneum of the skin play important roles for maintaining a barrier function and protecting the skin from harm.[43]

Ceramide Toxicity and Safety Data and Animal Studies

There have been numerous toxicology and animal studies of ingested Ceramide. The available toxicology and safety profile of this product offer ample assurances of the safety of Ceramide in clinical, ingested use. This conclusion can be drawn from the work of several researchers who examined both acute and chronic toxicity in animals.

Acute Toxicity

An LD 50 test was performed by SGTI's supplier, Ennagram, dated July, 1999



[41] Schmelz, Merrill 1989, Futerman, and Lati.

[42] Motta, S. *et al.*, Ceramide Compositions of the Psoratic Scale, Biochimica et Biophysica Acta, 1182: pp. 147-151 (1993).

[43] Imokawa, Lee, Goldstein, Lati and Chamlin.

[44] Ennagram's Vegetal Ceramides: LD-50 Study, dated July 1999; and Ennagram Report dated November 1997.

[redacted] [45] Again, by contrast, the amount of Ceramides in SGTI's proposed dietary supplement is only [redacted]

In addition to the LD 50, other animal tests were conducted on the ingredient, for example, an evaluation of acute toxicity in rats by oral route. [redacted] [46] This wheat Ceramide safety brochure also contained toxicity data, and the results were very similar to the rice-derived Ceramide studies because of the similarity between the components.

In a 1996 report, Richeux discusses administering CENNAMIDE CERO 15, a product name for a vegetal ceramide produced by Ennagram, to a group of 6 Sprague Dawley rats (3 males and 3 females) at a single dose of 5,000 mg/kg body weight per day for a week. This study was performed according to the experimental protocol established on the basis of the official method as defined in the O.E.C.D. guideline No. 423 dated March 22nd, 1996 and the test method B.1ter of the Directive No. 96/54/EC dated July 30th, 1996. The animals were administered the product by force-feeding under a volume of 5 ml/kg body weight using a suitable syringe (graduated), fitted with an oesophageal metal canula. No mortality occurred during the study. The conclusion was: LD_{50} of the product (REF.03.749 CENNAMIDE CERO 15) is higher than 5 g/mg by oral route in the rat. [47]

In 1989 Merrill reported the digestion and absorption of sphingomyelin, ceramide, and sphingosine using an *in vivo* intestinal loop technique with rats. This abstract reports that essentially no sphingomyelin or ceramide was hydrolyzed or lost from the small intestinal segments; however,

[45] Oryza Brochure at p. 8.

[46] Kenko Corporation In-house Report.

[47] Richeux, F., BioHC Appendix 2, Report to the Investigator TA0423-PH-03/0307 (1996); Appendix 2 (1997). [See cover letter of Report.]

digestion and uptake from the colon was evident. In addition, later work by Merrill, in 1997, confirmed and refined these results.[48]

Schmelz, in 1994, reported that radio-labeled sphingolipids were placed in isolated intestinal segments of female mice, and the metabolism and distribution of the radiolabel were followed.[49] The aim of the study was to determine if sphingomyelin can be digested and taken up by different regions of the intestine, with particular interest in determining if ceramide and sphingosine are formed. The study documents that a substantial portion of the sphingomyelin was cleaved to ceramide and sphingosine. Similar to information presented at the beginning of this Notification, this study reports that sphingomyelin is present in substantial amounts in milk (123 µmol/L), salmon (160 nmol/g), pork and beef tissue (350-390 nmol/g), and chicken (530 nmol/g). The study reports that there was substantial metabolism of sphingomyelin throughout the intestine. Ceramide was the primary breakdown product of sphingomyelin found in almost all regions of the intestine, accounting for up to 9.5% of the administered dose. No safety data is reported in the study.

Most recently, in 2002, Berra reports that sphingomyelin is hydrolyzed by a sphingomyelinase in response to extracellular stimuli, generating the lipid moiety ceramide and the water-soluble moiety choline-phophate. The study also reports that milk (lyophilized) contains several species of glycospingolipids, such as Mono-hexosylceramide, Lactosylceramide, and Tetra-hexosylceramide. No safety data is reported in the study, but its import lies in the careful documentation of the ubiquitous nature of Ceramides, in various forms, in conventional foods.[50]

Clinical Trials and Safety

Human clinical trials have been conducted on Ceramides as well. A double-blind placebo-controlled study was conducted at Osaka City University to evaluate the effects of oral

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[48] Merrill, A.H., Jr. *et al.*, Sphingolipid Uptake by Isolated Segments of the Rat Intestine, FASEB Journal, P. 3A, 469, 1989. Merrill, A., Importance of Sphingolipids and Inhibitors of Sphingolipid Metabolism as Components of Animal Diets, Journal of Nutrition, Vol. 127, pp. 830S- 833S, 1997 ("Merrill 1997").

[49] Schmelz.

[50] Berra, B. *et al.*, Dietary Sphingolipids in Colorectal Cancer Prevention, Eur. J. of Cancer Prev., Vol. 11, pp. 193-197, 2002.

administration of supplements containing rice ceramides in 33 patients with a habitual tendency toward dry, rough skin. The 33 patients were comprised of 6 men and 27 women, and the study was performed in keeping with the tenets of the Helsinki Accord, with written Informed Consent forms. This study was performed as a double-blind trial involving 6-week oral administration of "functional supplements" containing rice-derived Ceramides or a placebo.[51]

The test supplement was given in the form of soft capsules provided by Oryza Oil & Fat Chemical Co., Ltd., with a daily consumption of rice-derived Oryza Ceramide, 40 mg/day, containing rice-derived sphingolipids of 1.2 mg/day. Placebo capsules were administered that were identical in appearance and smell, but containing 0 mg/day of rice-derived Oryza Ceramide and 0 mg/day of rice-derived sphingolipids. After the 6-week trial period, no subjects had dropped out and no adverse events were reported. Other evidence of the safety of ingested Ceramides is also presented in this study:

> Experiments have shown that after oral administration plant-based ceramides are absorbed unchanged in the small intestine or are broken down into sphingosine and fatty acids for absorption and are then reconfigured as ceramides. The substance is then transported by the capillaries into the horny layer and the keratin intercellular spaces. The supplements containing rice ceramides as used in this study, in contrast to the ceramide substances distributed in animal brains, provide superior supplementation that can be expected to be both safe and effective for oral administration. [Emphasis added.][52]

Confirming this assessment is Lati, who as early as 1995 wrote about the use of ceramides in functional foods:

> Ceramide has been highly appraised in the field of functional foods because of its hydration characteristics and vectorization of vitamins (vitamin C and E).
>
> Presently phytoceramides by INOCOSM [Laboratories] are used as ingredients for various functional and cosmeceutical foods.
>
> Because of its hydration characteristics, ceramide is most extensively used in this field, and it is generally used together with vitamins.[53] . . .

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[51] Kajimoto, esp. at p. 2.

[52] Kajimoto at p. 12.

[53] Lati at p. 6.

Ceramide has shown numerous benefits as a food additive because of its very unique characteristics, and it is effective not only for the tissues but also for the stabilization of foods in some cases. If a certain amount of phytoceramide is ingested every day, the following benefits could be attained.

- Because ceramide suppresses free radicals, ceramide can enhance the protection of tissues from external harmful effects (pollution, sunshine, and stress).
- Ceramide moisturizes the skin by its hydration capability.
- Ceramide achieves wrinkle prevention by its elastase suppression and collagen protection.

. . . On the other hand, if ceramide is added to drinks for the benefit of the tissues, ceramide can also stabilize hydrophobic flavoring ingredients and hydrophobic molecules (vitamins) by vectorization.[54]

These conclusions are based in part on Lati's 1995 study which concludes that phyto-ceramides taken orally improve the hydration of the skin. The phyto-ceramides were given at an amount of 20 mg/day for a month. No adverse effects or events were reported.[55]

Ceramide Use Topically Moves to Ceramide Use Ingested

Ceramides have been traditionally found in topical formulas such as creams and lotions. Possibly the oldest exponent of an emulsifier free cream is the cold-cream. "Cold creams" contain structures which are similar to the bi-layers of the stratum corneum. Therefore Ceramide integrates in the skin barrier layers and it is very resistant against exogenous substances. It is recommended to avoid occlusive components on mineral oil base for this concept as they slow down the formation of the skin's own protective substances. This can be shown by artificially damaging the skin with adhesive tape strips (stripping). While the skin regenerates under normal conditions within 24 hours, the regeneration process is considerably delayed if the skin is artificially covered. [56]

Internal ingestion of Ceramide is a concept which takes the benefits of Ceramides for skin health and beauty to a new level. While a topical cream can provide only so much of a moisture layer, an internal formula can carry or transport Ceramides to the cell level, thereby increasing the

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[54] Lati at p. 11.

[55] Lati.

[56] Vesper, Imakawa, Lee, Goldstein, and Chamlin.

potential for a Ceramide product to be absorbed into the layers of the skin. One common sense indication that Ceramides are safe when ingested is that they have been included in semi-ingested products such as lipsticks for many years. Lipstick is a cosmetic used by millions of women in the U.S. that is gradually and eventually ingested throughout the day (because of the natural phenomenon of licking one's lips) and is reapplied continuously during the day as well. Although very hard to calculate, some amount of Ceramides in the "ingested" lipstick is consumed every day, assuming at least four re-applications per day.

A reasonable expectation of safety for ingested ceramides also may be deduced from at least three patents, two concerning lipsticks. A patent for a "Long wearing lipstick" includes a wax and "a phytosphingosine type ceramide."[57] In the detailed description of the invention, we learn that the invention calls for the phytosphingosine-type ceramide to be present in the lipstick, preferably from .20 to .50% by weight. According to the inventors, improved wear of the lipstick, without sacrificing gloss, increased from .1 % of Ceramide 3B to .2 and .5 % respectively. Human clinical trials were performed, in which the experimental ceramide-containing lipsticks were applied twice a day. While lipsticks are semi-ingestible, there are two other patents describing uses of ceramides in fully ingested products, and even pharmaceutical products, as well as topically-applied cosmetics.

In patent 6,136,301, "Lipid mix for lip product," one application is for an OTC drug lip balm.[58] This invention relates to a mixture of less than about 5% by weight of sphingolipids (including ceramides), for both cosmetic and pharmaceutical formulations for topical use on the lips. One claim is for a method of treating or preventing damage to the lips, and other therapeutic embodiments are described.

Finally, in patent 5,817,646, "Polar lipid composition of plant origin," the composition is comprised of "an injectable, intra-articular, topical or ingestible aqueous emulsion of a polar lipid mixture rich in phospholipids, in glycolipids and in ceramides. . ."[59] (emphases added).

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[57] Szweda, J.A. *et al.,* United States Patent 5,667,770, "Long wearing lipstick," issued Sept. 16, 1997.

[58] Pelle, E. *et al.,* United States Patent 6,136,301, "Lipid mix for lip product," issued October 24, 2000 ("Pelle" or '301 patent).

[59] Gossioux, P. United States Patent 5,817,646, "Polar lipid composition of plant origin," issued October 6, 1998 ("Gossioux" or '646 patent).

This mixture is obtained from cereal flour or an extract such as bran or lipids extracted from cereals, and thus is similar to the wheat-derived Ceramides discussed above, which is one type of Ceramide being the subject of this Notification. The mixture in this invention is 90% ceramides by weight, and the concept is to create a polar lipid mixture of plant origin essentially identical to the composition of the constituents of the target cells. The detailed description of the invention explicitly states (at page 7 of 14) that this polar lipid mixture can be used as a dietary supplement, in addition to uses for pharmaceuticals or cosmetics. It also notes that ceramides help with retention of water and thus aid in hydration of the skin. In addition, this invention may be applied to drug treatment: "as a vehicle for the delivery of a vaccine component"; and other tests were performed at the laboratories of the Faculty of Pharmacy of Chatenay Malabry (France).[60] This invention highlights the safety and efficacy of a ceramide product for targeting cells with a specific composition. (Copies of all patents attached.)

An internal formula containing Ceramide provides a cost effective way to get more Ceramide into the skin without the barrier of creams and lotions. Ceramides designed for ingestion work from the inside out rather than the traditional outside in methods of topical creams.

Plant Sterols, Chemically Similar to Ceramides, are GRAS for Foods

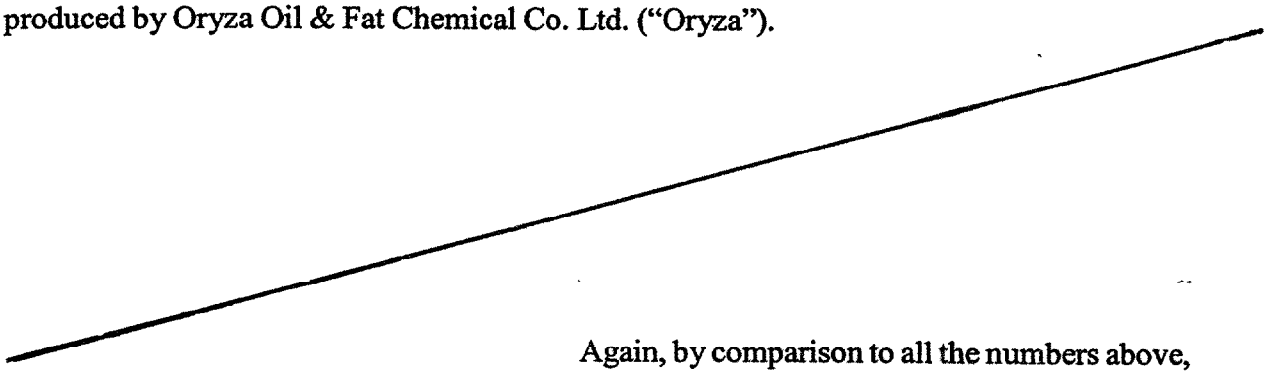
Another indication of the reasonable expectation of safety for a Ceramide supplement is by analogy to the safety profile of plant sterols. Plant Sterols are in the same chemical "family" as phyto-derived Ceramides. Fundamentally similar to Ceramides, which are a type of lipid or natural fat found in many foods, plant sterols or "plant fats" are present in virtually all fruits and vegetables. Indeed, plant sterols are substantially equivalent in their natural occurrence in conventional foods, and in the way in which they occur and are metabolized in the human body. Recently, the Food and Drug Administration ("FDA") has accepted a GRAS (Generally Recognized As Safe) petition from Cargill, Inc. for use of plant sterols in foods, and also has approved a health claim linking 1.3 g of plant sterols per day with a reduced risk of coronary heart disease. (See the FDA's Final Rule, 21 C.F.R. sec. 101.83.) Given the close chemical relationship between plant sterols and Ceramides, SGTI's Technical Department has concluded that this GRAS status of plant sterols and the FDA's official, pre-approved health claim logically indicates that if 1.3 g per day of plant sterols are

[60] Gossioux, at page 10 of 14.

considered safe (indeed beneficial) by the FDA, then 60 mg per day of Ceramides has a reasonable expectation of safety.

A History of Safe Use of Ceramides in Dietary Supplements in Japan

Two dietary supplements containing Ceramides derived from rice (=Oryza sativa) are produced by Oryza Oil & Fat Chemical Co. Ltd. ("Oryza").



Again, by comparison to all the numbers above, of Ceramide per day is the maximum recommended use of Ceramide in this Notification. Oryza Ceramide-P and Oryza Ceramide –L have been sold in Japan for approximately 5 years, and to our knowledge no adverse events have been reported.

In several Japanese Internet websites selling nutritional supplements, many different products containing phyto-ceramides are advertised.[62] Among these products is one called "Honen Ceramide & Cysteine," which contains ceramides extracted from the Konjac tuber, where a 4-capsule serving contains 24 mg of ceramide powder. The ceramide is extracted from Konjac tubers, a food that has been eaten by the Japanese since as far back as the Heian Period (794-1192), and that reportedly contains 7 to 15 times more ceramides than found in rice or wheat. The manufacturer of this particular ceramide nutritional supplement reports that the acute toxicity (LD_{50}) is

Also, the advertisement reports a survey in which Konjac ceramides are taken for 4 weeks. Finally, part of the promotion includes that the company's research has been presented at a Food Science conference:

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[61] Brochure entitled Oryza Ceramide, Nutritional Supplement, from Oryza Oil & Fat Chemical Co. Ltd, called in the footer: ORYZA CERAMIDE CATALOG ver. 1.0EZ ("Oryza brochure").

[62] Japanese promotional websites (excerpts), Winter 2003-2004.

> Unitika Ltd. ranks its Life Health business as one of its most important areas of business. At the end of last year, Unitika succeeded in extracting ceramides contained in the konjac tuber and is expecting to move into new markets with the commercialization of this highly purified, pure plant ceramide as a product with cosmetic and dietary applications.
>
> At the August 2002 Conference of the Japanese Society for Food Science and Technology, [Ceramide's] function as a new beauty food material was announced, and that it is a beauty ingredient that is attracting attention.

Indeed, the "collaborative campaign" by Honen Corporation and Unitika Ltd. launched its Ceramide product on November 17, 2002. The Unitika Ltd. brochure for the Konjac Ceramide Supplement stresses its safety and seems to imply use as a food additive as well:

> "Phyto-Ceramide" which is an extract from Konjac . . . is an edible beauty-care product richly containing Glucosylceramide, a Glycosphingolipid.
>
> Being natural products from Konjac, "Phyto-Ceramide" is a highly safe food, and continuous intake will gain high performance.
>
> As Phyto-Ceramide take on varied appearances, its usage is suitable to any kind of food.[63]

Another Japanese product advertised on the Internet is Morishita Jintan's "Collagen & Ceramide Concentrate Tablets," where one daily "pouch" contains 0.6 mg of ceramides. Further, three additional products are advertised on these websites, namely "Cell Este" (Product Number CER-1), "Sup. Ceramide" (Product Number CER-1), and Ozio's "Ceramide and Cysteine" (Product No. 010000016023). Promotions for these three products state that they contain ceramides and are to be ingested. Ozio's "Ceramide and Cysteine" advertisement states that it contains 75 mg ceramides in a daily dose. Clearly, for product liability reasons, if Ceramide supplements were unsafe at 75 mg of Ceramides per day, then this product would not be able to stay on the market.

Japan does have a counterpart to the Food and Drug Administration in the U.S., and this is called the Ministry of Health, Labor and Welfare. According to a report by International Business Strategies,[64] Japan has very strict limits on the substances allowed in dietary supplements: only 350 synthetic food additives and 490 natural origin additives may be used in food. This appears to require that dietary supplement ingredients, unlike in the U.S., must be GRAS, or at least officially

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[63] Unitika Ltd., CERAMIDE: Clears the skin as you eat. [Promotional brochure.]

[64] International Business Strategies, Dietary Supplements in Japan, December 2001.

on the "safe" list. Any substance not on the list may not be used in supplements. In addition, additives which have been approved for use in Japan in pharmaceuticals are not permissible for use in supplements unless they are on the list of 350 synthetic food additives. Japan's regulatory regime has been termed "both restrictive and opaque" by this report (at p. 5), which explains that many ingredients or products that may be sold in other countries may not necessarily be legal in Japan. For example, supplements from the U.S. routinely must be both reformulated and relabeled before they may be sold in Japan. Finally, it was not until April 1, 2001 that Japan implemented new regulations permitting health effect claims (cf. structure/function claims) on supplement labels. The main point here is that arguably the Ministry of Health, Labor and Welfare in Japan is much stricter in regard to nutritional supplements than is the FDA under DSHEA, and yet Ceramides are permitted as supplement ingredients in Japan, and have been on the market there for approximately five years.

Conclusion of Reasonable Expectation of Safety

Under 21 C.F.R. § 190.6 (a), the standard for a new dietary ingredient premarket Notification is that the manufacturer presents the basis on which it has concluded that "a dietary supplement containing such dietary ingredient will reasonably be expected to be safe." In this Notification, we have documented a reasonable expectation of safety for a dietary supplement containing phyto-derived Ceramides, at the amount of ——————————— in five ways: 1) the presence of Ceramides in much larger amounts in ordinary foods that make up the human diet and that are consumed daily; 2) two toxicity studies showing that the LD 50 is more than 5,000 mg/kg; 3) clinical trials on rats and humans demonstrating no mortality or toxicity, safety, and no adverse events; 4) a very similar substance (plant sterols) accepted as being GRAS, clearly a much higher standard of safety; and 5) dietary supplements marketed and consumed in Japan containing Ceramides at the same or higher levels than for the proposed SGTI product, in a country that regulates supplements more rigorously than in the U.S. In addition, as stated above, Ceramides are naturally present in human skin, the central nervous system, and spinal marrow. Copies of all articles and reports cited herein are attached, pursuant to 21 C.F.R. § 190.6 (b)(4). Together, these articles and reports, in conjunction with the facts, data, and analysis above, demonstrate that a dietary supplement containing phyto-derived Ceramides at the level of , and under the conditions of use above, will reasonably be expected to be safe.

Note on Confidentiality

In order to present full background on this NDI, this Notification contains proprietary information and trade secrets of SGTI, and thus is the Confidential version of the submission. Pursuant to 21 C.F.R. sec. 190.6 (e), SGTI, through its counsel, Susan Brienza, Esq. of Patton Boggs LLP (Denver Office), reserves the right to redact all commercial confidential, proprietary and trade secret information within 90 days of this filing, and to provide that redacted version to this office, before the Notification is publicly displayed or added to the FDA's public Docket.

SOFT GEL TECHNOLOGIES, INC.

By: Ronald Udell

Ronald G. Udell, President

Date: March 26, 2004

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Phyto-derived Ceramides

New Dietary Ingredient Notification - Attachments (under 21 C.F.R. Sec. 190.6)

Attachments cited in the footnotes and references of the New Dietary Ingredient Notification for Phyto-derived Ceramides: These have been ordered alphabetically by author's last name, and if there is no author, by the source or title of the article.

Submitted by: Soft Gel Technologies, Inc.

April 2, 2004